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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,640	12/01/2008	Zhaohui Peng	U 016018-5	4272

140 7590 03/23/2011

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
03/23/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/556,640	PENG ET AL.	
	Examiner	Art Unit	
	SHIN LIN CHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5 and 8-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 1-10-11 has been entered. Claims 4, 5, 8 and 9 have been amended. Claims 1-3, 6 and 7 have been canceled. Claim 10 has been added. Claims 4, 5 and 8-10 are pending and under consideration.

Specification

It appears that the specification filed 11-10-05 contains the intended amendment on the specification pages 1, 2, 4, 6 and 7 in the amendment filed 12-1-08. Changing the specification back to the specification filed 11-10-05 would be remedial. It should be noted that the amendment of adding "SEQ ID No. 1" on page 4 of the amendment on specification filed 1-10-11 should be maintained.

This application contains sequence disclosures that are encompassed by the definition for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there is no sequence identifier for the nucleotide sequence on pages 8, 10 and 12 of the specification or in the "BRIEF DESCRIPTION OF THE DRAWINGS". Each nucleotide sequence is required to have a sequence identifier. Appropriate correction is required.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 4, 5 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's amendment filed 1-10-11 necessitates this new ground or rejection.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 4, 5 and 8-10 are directed to a method for treating a scar comprising administering to a patient a recombinant of adenoviral vector and human suppressor p53 gene

expressing cassette comprising RSV LTR promoter-5'cis-acting sequence-p53cDNA-3' cis-acting sequence-polyadenosine. Claims 4 and 5 are directed to production of the recombinant adenoviral vector by using homologous recombination between pGT-1 plasmid and adenovirus in prokaryotic cells to produce pGT-2, and homologous recombination of pGT-2 and an artificial sequence containing the right arm of adenovirus/promoter-p53-poly A/ the left arm of adenovirus in prokaryotic cells, such as E. coli, wherein the prokaryotic sequence is discarded by suing endonuclease PacI. Claim 8 specifies the pathological scar is cheloid. Claim 9 specifies the recombinant adenoviral vector is administered by injection.

The specification discloses "the size of the scar had significantly decreased after gene therapy for 4 weeks" (page 14, Experiment 3). The specification fails to disclose what kind of "gene therapy" has been performed and how the therapeutic gene is administered in vivo. The claims encompass administering a recombinant adenoviral vector containing a p53 gene for treating various scars, including cheloid, at different locations in a subject via various administration routes in vivo. The specification fails to provide adequate guidance and evidence for how to treat various scars, including cheloid, at different locations in a subject via various administration routes so as to provide therapeutic effect in vivo.

The claims read on gene therapy by using the claimed recombinant adenoviral vector in vivo. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer in vivo, vector targeting to desired tissues in vivo continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to

target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma et al., Sept. 1997 (Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). The claims encompass using various promoters for the expression of the p53 polypeptide at various target cells in a subject. Different promoters have different activity in stimulating gene expression in different cells in vivo and whether there is sufficient expression of the p53 polypeptide at target cells depends on what promoter is used.

Administration route also plays a very important role in determining whether sufficient p53 polypeptide can be expressed and present at the target cells at various locations in vivo. The phrase "administered by injection" in claim 9 reads on various administration routes, such as intravenous administration, intramuscular injection, and intraperitoneal injection etc. The administration route includes direct administration to the target cells, oral administration, intraperitoneal injection, topical administration, intravenous administration, intramuscular injection, and subcutaneous administration etc. There are various barriers before a nucleic acid construct can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) reports that numerous factors

complicate in vivo gene transfer with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e,g, bridging pages 81-82). Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy in vivo include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). In addition, Thomas et al., 2003 (Nature Reviews/ Genetics, Vol. 4, p. 346-358) discusses the problem of viral vector in gene therapy. Thomas reports that "adenovirus vectors induce multiple components of the immune response: cytotoxic T-lymphocyte (CTL) responses can be elicited against viral gene products or "foreign" transgene products that are expressed by transduced cells, and the capsid itself--- in the absence of viral gene expression --- induces humoral virus-neutralizing antibody responses and potent cytokine-mediated inflammatory responses (e.g. p. 352, right column). There is no evidence of record that demonstrates administration of a recombinant adenoviral vector encoding p53 via various administration

routes would result in sufficient expressed p53 protein at target sites in a subject so as to provide therapeutic effect for treating various scars in vivo. Absent specific guidance, one skilled in the art at the time of the invention would not know how to use the claimed recombinant adenoviral vector for treating various scars, such as cheloid, at different locations in a subject via various administration routes in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicant cites Examples 2-3 and Figures 8-9, and argues that the recombinant adenoviral vector containing p53 exhibits a substantive killing effect to fibroblast cells in vitro. A clinical study has been carried out for keloid and all kinds of scar can be medically treated with recombinant adenoviral vector containing p53 in view of the in vitro test (amendment, p. 8). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112, first paragraph. The killing effect of fibroblast cells by the adenoviral vector expressing p53 in vitro cannot be extrapolated into the in vivo effect in treating various scars. As discussed above, the claims encompass administering a recombinant adenoviral vector containing a p53 gene for treating various scars, including cheloid, at different locations in a subject via various administration routes in vivo. The specification fails to provide adequate guidance and evidence

for how to treat various scars, including cheloid, at different locations in a subject via various administration routes so as to provide therapeutic effect in vivo. The claims encompass using various promoters for the expression of the p53 polypeptide at various target cells in a subject. Different promoters have different activity in stimulating gene expression in different cells in vivo and whether there is sufficient expression of the p53 polypeptide at target cells depends on what promoter is used. Administration route also plays a very important role in determining whether sufficient p53 polypeptide can be expressed and present at the target cells at various locations in vivo. There are various barriers before a nucleic acid construct can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids. There is no evidence of record that demonstrates administration of a recombinant adenoviral vector encoding p53 via various administration routes would result in sufficient expressed p53 protein at target sites in a subject so as to provide therapeutic effect for treating various scars in vivo. Absent specific guidance, one skilled in the art at the time of the invention would not know how to use the claimed recombinant adenoviral vector for treating various scars, such as cheloid, at different locations in a subject via various administration routes in vivo. The specification also fails to disclose what kind of "gene therapy" has been performed and how the therapeutic gene is administered in vivo. There is only Figure 10 but no Figure 10A and 10B. The right panel (After treatment) of Figure 10 appears to show much larger dark area than the left panel (Before treatment). It is unclear whether the recombinant adenoviral vector expressing p53 can reduce the cheloid in vivo or not. The specification fails to show that the cheloid or

various scars can be treated with a recombinant adenoviral vector expressing p53 in vivo. Thus, the claims are rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 9 recites the limitation "the pathological scar" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Claim 9 depends from newly added claim 10, which does not recite pathological scar. Applicant's amendment filed 1-10-11 necessitates this new ground of rejection.

Conclusion

No claim is allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Shin-Lin Chen/
Primary Examiner
Art Unit 1632